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Atherosclerosis: An update

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Epidemiologic studies have identified risk factors for coronary heart disease (CHD) and its underlying pathologic condition: atherosclerosis. Genetic and environmental factors interact to shape an individual's age-related risk of atherosclerosis.[1-6] In the Framingham study, there was a positive correlation between CHD risk and low-density lipoprotein cholesterol (LDL-C), total cholesterol,[4] and total cholesterol high-density lipoprotein (HDL)-C ratio.[7] A weak correlation exists between CHD and triglyceride (TG),[7] and cholesterol[8] levels, hypertension,[9] obesity,[10] diabetes,[11] smoking,[12] and left ventricular hypertrophy,[13] and an inverse correlation with HDL-C.[14] Hyperinsulinemia may also promote the development of many of these CHD risk factors.[15, 16] Plasma insulin levels have been positively associated with CHD incidence,[17] and fasting insulin and insulin/glucose ratio have been shown to be independent risk factors for coronary artery disease incidence.[17, 18] Another modifiable risk factor is smoking and even passive smoking has been shown to increase experimental atherosclerosis.[19] Many of these risk factors are interconnected. For example, severe large vessel disease in men is associated with smoking, plasma glucose levels, and systolic blood pressure.[20]

Other measurable factors are receiving increasing attention as cardiovascular (CV) risk factors. Elevated fibrinogen levels appear to be a relatively potent risk factors for CHD.[21] White blood cell (WBC) count has been positively correlated with the risk of atherosclerosis;[21, 22] this correlation is partially accounted for by smoking (in a dose-dependent manner).[22] In this regard, certain chronic infections, such as herpes infection, have been associated with an increased risk of atherosclerosis.[23] In contrast, increasing attention and research is being devoted to antioxidants such as vitamin C and even garlic as protective factors against atherosclerosis.[24, 25]

PATHOLOGIC FEATURES OF ATHEROSCLEROSIS

Atherosclerotic lesions consist of[26-28] (1) the *fatty streak*, found in childhood, consists of lipid accumulation (cholesterol, cholestryl ester) in macrophages (MP), T lymphocytes, and smooth muscle cells (SMCs)[27, 28] in addition to ingested lipoprotein-proteoglycan complexes in more complex foam cells[16, 27, 28], (2) the *fibrous plaque*[16, 26-28] consists of a lipid core surrounded by a fibrous cap that results from the synthesis of collagen, elastin, and proteoglycans by SMCs and MP that have migrated to the intima.[16, 27, 28]

The atherosclerotic process begins, according to the response-to-injury-hypothesis, with a structural or functional injury to the endothelium, resulting in increased permeability of the endothelial barrier to blood cells, hormones, and lipoproteins.[27-29] Platelets, aggregating at the site of injury, release growth factors and chemoattractants that stimulate the proliferation of SMCs and the migration of SMCs and MP to the subintima region where the atherosclerotic process develops.[16, 26-29]

PATHOGENESIS OF ATHEROSCLEROSIS

The pathogenesis of atherosclerosis is reviewed from the perspective of several different mechanisms.

Growth and atherosclerosis. The natural history of atherosclerosis may be viewed from the *growth* perspective.[28, 29] This can be summarized as follows:

1. Developmental origins. The vessel wall mass is genetically determined at birth. Endothelial cells (EC) initiate differentiation of SMCs from locally derived mesenchymal cells, making the uniformity of the SMC phenotype problematic: undifferentiated cells appear postnatally in the intima as part of normal development and as a prominent feature of atherosclerotic lesions that begin early in development with the focal proliferation of these cells.

2. Focal proliferation: Monoclonality. A large proportion of atherosclerotic plaques of human vessels

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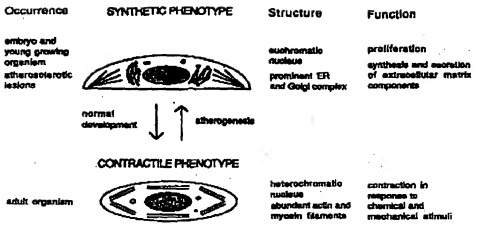

Fig. 1. Schematic representation of different characteristics of arterial smooth muscle cells in synthetic vs contractile phenotypes. *ER*, Endoplasmic reticulum. (From Sarzani et al. Hypertension 1991;18[suppl III]:93-9.)

appear to be of monoclonal origin, suggesting the possibility that monoclonality develops during embryogenesis with accelerated growth of preexisting intimal cell masses. Monoclonality may develop also as a result of repeated replication of rare SMCs that are trapped in the intima or migrated SMCs from the media under the influence of locally released mitogens.[28] In contrast, hyperplastic polyploid focal proliferation occurs under certain conditions such as the hypertensive process.[29]

3. Formation of the classical lesion. Fatty metamorphosis occurs, and the intimal atherosclerotic lesion develops a central fatty necrotic mass covered by a fibrous cap.[16, 28] The evolution of this lesion is first that of fat-filled MP with SMC accumulation in the intima, occurring as a secondary event resulting from mitogens released from MP, platelets, or dying cells (i.e., from lipid peroxidation products). Monocytes promote the atherosclerotic process by producing platelet-derived growth factor (PDGF) and other mitogens that exponentially increase the migration of other monocytes and the uptake of LDL-C to form foam cells. Subsequently, platelets aggregate at sites where the endothelium breaks down (over accumulated MP and on exposed subendothelium), releasing heparitinase, platelet factor 4, and PDGF, which further promotes the atherosclerosis process.[16, 28]

4. Conversion of the classical lesion into a complex lesion. This process involves such mechanisms as occlusive thrombosis, plaque rupture, and vasospasm.[16, 28] These complex atherosclerotic plaques become more calcified and consist of a substantial connective tissue matrix with central fatty necrosis. Progression of the thrombotic process and plaque rupture lead to the clinical events associated with these complex lesions.[16, 28]

Specific constituents of atherosclerotic lesions. Two major phenotypes of arterial SMCs have been described[26-28] (Fig. 1): (1) the *contractile* phenotype is found in arterial media, contains myofilaments, and is responsible for contraction and relaxation of the vasculature; and (2) *synthetic* SMCs found in the intima during the atherosclerotic process after the migration of contractile SMCs from the media; the synthetic cells proliferate, take up LDL-C, and synthesize abnormally large amounts of collagen, elastin, and proteoglycans.[28, 29] Thus SMCs that are contractile in the media become phenotypically different on migrating to the intima. The polyamines putrescine, spermidine, and spermine are involved in the transition of these migrated SMCs into a synthetic phenotype.[29]

Mitogens and growth factors in atherosclerosis. A number of mitogens and growth factors play an important role in the atherosclerotic process. One of these, PDGF, is present in three isoforms (AA, AB, BB), which interact with several different cell receptors.[30] PDGF provokes a rapid and transient rise in intracellular calcium $[Ca^{2+}]_i$ and a slower more substained enhancement of DNA synthesis in SMCs.[31] Thus PDGF enhances the proliferation and migration of SMC[32] (Fig. 2). PDGF may interact also with other growth factors, such as insulin-like growth factor-1 (IGF-1), to enhance SMC proliferation and migration.[33] Infusion of the BB isoform of PDGF into rats subjected to carotid injury produces a twofold to threefold increase in medial SMC proliferation but a 20-fold increase in intimal thickening and SMC migration from media to intima within a week after in-

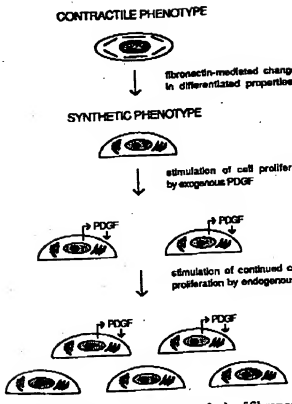

Fig. 2. Schematic representation of role of fibronectin and PDGF in transition from contractile to synthetic phenotypes and in proliferation of arterial smooth muscle cells. (From Sarzani et al. Hypertension 1991;18(suppl III):93-9.

jury.[34] SMCs isolated from intimal lesions after balloon catherization synthesize significantly greater amounts of PDGF than do SMCs isolated from normal media. PDGF-receptor activity also increases when SMCs change to a synthetic phenotype.[35] Both PDGF and epidermal growth factor (EGF) then interact to further promote migration of SMC to the intima and subsequent proliferation of these migrated cells.[35]

PDGF gene expression is low in the normal vascular wall tissue and high in sites prone to SMC proliferation such as the intima of atherosclerotic plaques.[26, 35] Different isoforms of PDGF display different effects on SMC proliferation.[36, 37] PDGF AA is a poor mitogen for SMC; however, it acts synergistically with fibroblast growth factor (FGF) to promote DNA syntheais.[28] This synergistic action results because FGF selectively increases PDGF-receptor expression and translation.[38, 39] The observation that in vivo expression of the PDGF increases with aging suggests that the interactive role of PDGF and FGF in the vasculopathy is associated with the aging process.[40]

Insulin-like growth factors (IGF-1 and IGF-2) and insulin appear to have an important role in the pathogenesis of atherosclerosis[41] (Fig. 3). For example, IGF-1 has been shown to stimulate ^{3}H-thymidine incorporation by vascular smooth muscle cells (VSMCs) in our laboratory (Fig. 4). Arterial injury is accompanied by a rapid and long-lasting induction of SMC IGF-1 messenger RNA (mRNA) expression.[41] Platelets express both IGF-1 and IGF-2, the expression being localized to the alpha granules. Platelets also have IGF-1 receptors, and platelet adherence and degranulation (activation) leads to the release of IGF.[41] Macrophage precursors also have IGF-1 receptors, and IGF stimulates the proliferation of these cells and their conversion into multinucleated cells.[41] Vascular SMCs express receptors for IGF-1, IGF-2, and insulin; however, the processing of IGF and insulin is different.[41, 42] IGFs also stimulate the proliferation of EC. Cells from microvascular and macrovascular beds differ in their mitogenic responsiveness to IGF-1 and IGF-2. For example, retinal vessel EC respond more than do aortic EC.[41] EC produce IGFs, and EC dysfunction may lead to increased release of IGFs, which, in turn, may promote neointimal VSMC proliferation.[41]

Expression of vascular SMC IGF-1 receptors varies with SMC growth status: in nonconfluent SMCs, insulin binding is low and IGF-1 binding is high, whereas the opposite is true in confluent cells.[41] PDGF and IGF-1 interact positively in inducing the expression of the protooncogene c-*myc* in cultured bovine vascular SMCs and in promoting cell growth.[41] Although insulin does not increase the mitogenic effect of IGF-1, the mitogenic response of insulin is mediated, in part, through an IGF-1 receptor.[41] Insulin has been shown to increase IGF gene expression in aortic SMCs.[41] Further, in insulin-deficient diabetic rats,[42] aortic IGF-1 mRNA abundance is significantly reduced compared with that in nondiabetic rats. Infusions of insulin into the aorta resulted in a twofold increase in IGF-1 mRNA in aorta, indicating that hyperinsulinemia might play its role in atherogenesis, in part, through enhanced expression of IGF-1 in the vessel wall.[42] Insulin alone or with PDGF does not appear to have a significant effect on SMC migration.[42, 43] However, SMC migration induced by the cyclooxygenase product 12-hydroxyeicosatetraenoic acid (HETE) is increased in relation to the concentration and duration of exposure to insulin.[44] This effect is augmented by increasing glucose concentration.[43]

IGFs, lipoproteins, and insulin are abundant normally in plasma, so the possibility arises that these factors are important also in vivo.[2, 15, 42, 45, 46] The effect of platelet extract on growth of rat aortic SMCs

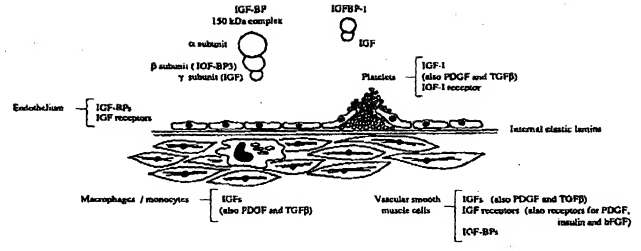

Fig. 3. Expression of IGFs and IGF BP in atherosclerotic plaque. (From Fern et al. Artery 1991;18:197-225.)

was observed to be higher in diabetic patients than in controls and was corrected with intensive insulin treatment.[47] On the other hand, it has been suggested that high circulating levels of insulin associated with insulin resistance could mediate tissue growth, perhaps through intact IGF-1 receptors.[43, 48] Aortic endothelium has the capacity to rapidly internalize and release insulin with minimal degradation.[44] Similar experiments with IGF-2 have demonstrated that there is a greater channeling of IGF-2 than of insulin into a degradative pathway within these cells.[49] These collective data suggest that IGF and perhaps insulin have atherogenic potential through effects exerted on vascular SMCs and EC.[43]

EGF has been shown to be secreted by platelets and to stimulate proliferation of SMCs in culture.[52] It appears that the growth effects of EGF are mediated, in part, through stimulation of a rise in SMC $[Ca^{2+}]_i$.[52] Further, the calcium channel blocker nifedipine suppresses the enhancement of vascular SMC DNA synthesis induced by EGF.[52] Vascular SMCs from spontaneously hypertensive rats (SHR) respond more to EGF than do those of normotensive rats, despite similar responsiveness to PDGF and IGF-I.[50] SMCs from SHR express twice the number of EGF receptors of those from their normotensive counterparts.[50] Further, cultured mesenteric and aortic myocyte growth response to EGF is enhanced in SHR.[51, 52] The VSMC proliferative effects of EGF are potentiated by insulin, suggesting that factors such as hypertension and hyperinsulinemia may be synergistic in promoting the atherogenic process.

Transforming growth factor beta (TGF-β), produced by VSMC,[53] endothelial cells,[53] macrophages,[54] T lymphocytes,[53] and platelets,[55] may have modulating effects on the atherosclerotic process. TGF-β has been shown to decrease proliferation of vascular SMCs despite induction of cellular hypertrophy.[56] However, TGF-β can stimulate SMC growth as well.[28] Its net effect on SMC growth depends, in part, on its ability to stimulate formation of appropriate kinds of extracellular matrix.[28, 53] Its effects also depend on the cell type involved. For example, TGF-β decreases EC migration and proliferation and increases SMC migration.[32] TGF-β stimulates expression of PDGF-A chain mRNA and secretion of PDGF-like molecules.[35] Hypertension and aging increase in vivo expression of TGF-β_1 in aortic tissue;[40] however, the relevance of these changes remains poorly understood.

Fibroblast growth factors. FGF type 1 and 2 are expressed in EC and SMCs.[28, 57] FGF plays an important role in control of SMC replication whenever cell injury has occurred.[28] FGF stimulates growth in quiescent SMCs in culture.[28, 58] Thus the precise role of FGF is incompletely understood.

Hormonal factors such as catecholamines influence the atherogenic process.[59] Repeated hypothalamic stimulation and consequent sympathetic discharge result in episodic vasospasm and injury to endothelium and media, as well as SMC proliferation, favoring the onset of atherogenesis.[59] The role of catecholamines is supported by the results of behavioral investigation in animal populations along with the clinical studies implicating neuropsycho-

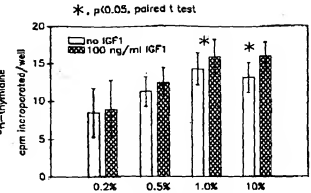

Fig. 4. Effect of IGF-1 100 ng/ml on thymidine incorporation in presence of different FBS concentrations in vascular smooth muscle cells from lean Zucker rat aortas (unpublished data).

logical mechanism in atherosclerosis.[59] Thus the sympathetic nervous system plays an important role in the pathogenesis of atherosclerosis and hypertension.

Norepinephrine and histamine increase EC proliferation and increase SMC proliferation and migration.[32] Epinephrine also stimulates proliferation of vascular SMC, and α-agonists stimulate PDGF-A chain gene expression.[32, 58] Angiotensin II also stimulates expression of PDGF-A chain mRNA, secretion of PDGF-like molecules, and vascular SMC hypertrophy.[32, 58] Endothelin may act as a growth factor for vascular SMCs, and this effect appears to be enhanced in the presence of insulin.[60] Endothelin also enhances Na/H exchange in conjunction with its proliferative effects on vascular SMCs.[60] Early changes in Na/H exchange are the same for endothelin, angiotensin, and PDGF, whereas late changes are different.[60, 61] Raised intracellular pH results in the activation of protein synthesis in quiescent aortic SMCs.[61, 62] Thus many vascular growth factors such as endothelin, angiotensin, and other serum factors may exert their atherogenic effects, in part, by stimulating Na/H exchange and raising intracellular pH.

The cytokines interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) are produced by macrophages.[63, 64] Both of these cytokines inhibit endothelial cell growth and stimulate SMC growth; this effect correlates with changes in FGF receptor number displayed by endothelial and SMC, respectively.[65] IL-1 promotes growth of vascular SMCs via induction of synthesis of PDGF with no effect on intracellular Ca^{2+}.[66] Another cytokine, IL-6, induces an increase in SMC thymidine uptake and proliferation.[67]

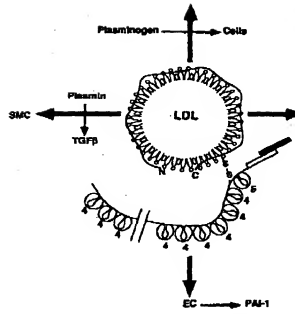

Fig. 5. Lp(a) and atherosclerosis. Lp(a) promotes thrombogenic phenotype at cell surface by competition for plasminogen receptor and enhanced production and secretion of PAI-1 with downregulation of plasmin generation. Fibrin deposition is increased on and in intima and SMC. SMC proliferation is promoted by inhibition of TGF-β activation and may contribute to atherogenesis. (From Nachman RL. Blood 1992;79:1897-906.)

IL-6 also stimulates PDGF production, and the SMC proliferative effects of this cytokine are inhibited by PDGF antibody (as measured by thymidine uptake).[67] These results indicate that IL-6 has an autocrine function through stimulation of PDGF production.[67] Another cytokine, smooth muscle–derived growth factor (SDGF) has been shown to be distinct from competent and progression factors and to stimulate different pathways in SMCs.[68] Thus cytokines have a profound and complex effect on SMC proliferation and thus the atherogenic process.

Metabolic factors and atherosclerosis. Central fat distribution may be atherogenic, in part, because of associated alterations in insulin and lipoprotein levels. For example, men and women with predominantly upper-body obesity have significantly higher insulin and glucose concentration after an oral glucose tolerance test.[69, 70] In regard to this observation, hypertrophic fat cells predominate in upper-body fat, and these fat cells demonstrate insulin resistance.[71] Central-body fat is also more metabolically active, showing increased lipolysis and release of free fatty acids (FFAs), which may interfere with insulin clearance and exacerbate hypertriglyceridemia.[72] Plasma insulin concentration, in turn, is an impor-

tant predictor of HDL-C decreases and TG concentration increases.[73] Waist/hip circumference ratio is a better marker than body mass index of risk of cardiovascular death in older women.[74] Thus central obesity is associated with insulin resistance, dyslipidemia, and increased risk of atherosclerotic vascular disease.[75]

Lipoprotein abnormalities and atherosclerosis. Macrophages express LDL receptors that recognize Apo B- and Apo E–containing lipoproteins. LDL receptors are downregulated by intracellular cholesterol.[76] Other receptors can mediate the uptake of altered lipoproteins: Scavenger receptors recognize modified lipoproteins such as acetylated LDL, oxidized LDL, or malondialdhyde LDL.[77, 78] Scavenger receptors recognize other negatively charged substances in a nonregulated way, leading to massive lipid accumulation.[76] The Fc receptor can mediate the uptake of lipoprotein–antibody complexes, resulting in lipid accumulation,[76] and the receptor for advanced glycation end products mediates uptake of glycated lipoprotein.[78] Non–receptor-mediated uptake of lipoprotein by macrophages can occur by phagocytosis[78] or through secretory enzymes released by macrophages.[76] The most important of these enzymes is lipoprotein lipase, which hydrolyzes TG to FFAs, which can be taken up by macrophages and reesterified, resulting in marked TG accumulation.[79, 80] The enhancement of receptor-mediated TG-rich lipoprotein uptake is caused by at least two factors: (1) conformational changes in apoproteins, resulting in increased affinity for LDL receptor,[80, 81] and (2) loss of Apo C.[79] In addition to lipoprotein lipase, macrophages secrete oxygen-free radicals, proteases, and Apo E, all of which affect lipoprotein accumulation.[76, 77]

Lipoprotein modification takes place in SMCs, EC, and macrophages. One such modification consists of peroxidation of polyunsaturated fatty acids in LDL, a process that can be inhibited by vitamin E.[82] The oxidized fatty acid fragments and sterols diffuse out of LDL into adjacent cells to exert chemotaxis and trapping of monocytes into the atherosclerotic lesion as MP. Oxidized LDL also alters gene expression for and secretion of growth factors and cytokines by MP and EC.[83] EC production of colony-stimulating factors is enhanced after incubation with oxidized LDL. Oxidized LDL is a chemoattractant to monocytes, induces monocyte-binding protein, and stimulates production of monocyte chemotactic protein (MCP-1) by endothelial cells. Oxidized LDL may be taken up by MP through scavenger receptors, phagocytosis, and Fc mediation of LDL-ICs (immune complexes), and induce paradoxical increase of LDL-receptor expression. Uncontrolled diabetes is accompanied by increased lipid oxidation. LDL oxidation is enhanced in the presence of hyperglycemia and hypertriglyceridemia. Hyperglycemia, in part through glycation products, enhances free-radical production in stimulated inflammatory cells. The mechanism of injury induced by oxidized LDL is related to the cell cycle: Fibroblasts in the S phase appear most vulnerable in vitro, and native HDL reduces the toxic effect of oxidized LDL to fibroblasts. A variety of other cells also appear to be vulnerable to the cytotoxic effects of oxidized LDL.[83]

One of the first endothelial alterations induced by LDL-C is an attenuation of endothelium-dependent vasodilation that occurs before any clinical evidence of atherosclerosis.[84] Isolated vessels from normal animals manifest a reduction in endothelium-dependent vasodilation within minutes of exposure to oxidized LDL.[85, 86] Lysolecithin in oxidatively modified LDL contributes significantly to its vasomotor effect.[87, 88] Insulin and IGF-1 cause an upregulation of LDL receptor and downregulation of HDL recep-

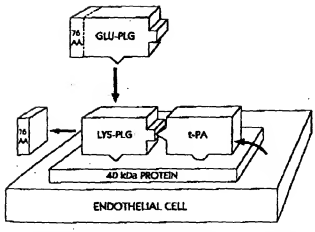

Fig. 6. Hypothetical model of plasminogen and tissue plasminogen activator *(tPA)* assembly on endothelial cell surface. On binding to endothelial cell surface, circulating N-terminal glutamic acid plasminogen is converted to its truncated, noncirculating form, N-terminal lysine plasminogen, through the proteolytic release of a 76aa preactivation peptide (76AA). Lys-PLG binds with high affinity to 40-kDa cell surface–associated protein. tPA, synthesized and secreted by endothelial cell, can bind to same protein at a separate domain. Assembly of plasminogen and tPA in complex with the 40-kDa protein on cell surface would foster efficient generation of plasmin-lipoprotein (a), in sufficient concentration, would compete with plasminogen for its binding site on the endothelial surface, thereby dampening production of active protease. (From Shih GC, Hajjar KA. Plasminogen and plasminogen activator assembly on the human endothelial cell. Proc Soc Exp Biol Med 1993;202:258-64.)

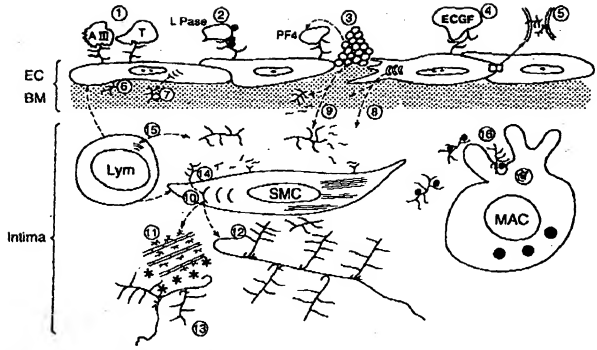

Fig. 7. Schematic representation of the different roles of proteoglycons in arterial wall biology. *1*, binding of coagulation and anticoagulation factors; *2*, Binding and regulation of enzyme (LPase) activity; *3*, carrier molecule for certain platelet products and plasma proteins; *4*, binding and regulation of growth factor activity; *5*, influencing cell–cell associations; *6*, influencing cell adhesion; *7*, participating in the organization of ECM structures such as basement membranes and regulating permeability; *8*, influencing endothelial cell migration and proliferation; *9, 14, 15*, modulation in arterial SMC proliferation and migration; *10, 11*, regulation of collagen fibrillogenesis; *12*, maintenance of viscoelastic properties; *13*, modulating calcification; *16*, influencing intra- and extracellular lipid deposition and turnover: *EC*, endothelial cells; *BM*, basement membrane; *AIII*, antithrombin III; *T*, thrombin; *LPase*, lipoprotein lipase; *PF4*, platelet factor 4; *ECGF*, endothelial derived growth factor; *Lym*, lymphocyte; *SMC*, smooth muscle cell; *MAC*, macrophage. (From Rasmussen et al. Arch Intern Med 1989;149:1050-3. Copyright 1989 American Medical Association.)

tor.[41] Insulin increases uptake and esterification of LDL-C by SMCs.[16] Thus both hyperinsulinemia and increased oxidation of LDL-C likely contribute to the accelerated atherosclerosis of diabetes mellitus. The role of antioxidants in the prevention of atherogenesis has been extensively reviewed.[25] Antioxidants protect LDL against oxidation: these include vitamin E, vitamin C, 17β-estradiol, and magnesium.[25, 89, 90] These antioxidants may have a particularly important prophylactic role in diabetic patients, who are especially prone to LDL oxidation.

The role of Lp(a) has been extensively reviewed (Figs. 5 and 6).[91, 92] Lp(a) is an LDL-like particle with Apo B-100 and Apo (a) components; the latter is similar to plasmin.[92] Large amounts of Lp(a) are found in atherosclerotic lesions. In early atherosclerotic lesions in human beings and animals, there is a dramatic deposition of Lp(a) on the thickened intimal endothelial surface. Lp(a) competitively inhibits binding of plasminogen, downregulates plasmin generation at the cell surface by 90%, and facilitates deposition of cell-surface and matrix lipoprotein. Normal vasculature does not contain Lp(a), and the vascular content of Lp(a) increases with various inflammatory conditions. Lp(a) increases Plasmogen activator inhibitor-1 (PAI-1) expression, and surface activation of plasminogen on macrophages and SMCs significantly contributes to their migration to the intima, where the atherosclerotic process develops.[92] Lp(a) may also promote enhanced intimal deposition of Apo B–containing lipoproteins, facilitating plaque formation.[91, 92] Plasmin enhances the binding of Lp(a) to immobilized fibrinogen and fibrin, leading to increased incorporation of fibrin into vessel wall.[92] Lp(a) in tissues may promote SMC migration by downregulating plasmin generation at the cell surface and thereby inhibit latent TGF-β activation. Lp(a) may thus indirectly increase SMC migration,

as TGF-β normally inhibits this process.[92] Apo(a) has antithrombolytic potential because of its plasminogen-like properties at the endothelial and subendothelial intima: (1) at the endothelial surface, high plasma levels of Lp(a) can interfere with plasminogen–plasmin conversion and clot lysis[93]; (2) Lp(a) can traverse endothelium and accumulate in intima as lipid-poor Apo B-100–Apo(a) complex or free Apo(a).[92] High Lp(a) plasma levels and increased endothelial permeability increase the transfer of Lp(a) to the intima.[91] Once in the intima, Lp(a) can complex with glycosaminoglycans, proteoglycans, or fibrin.[94] Lp(a) also becomes incorporated into MP in the intima, leading to formation of foam cells.[85] Thus Lp(a) appears to be an important factor in promoting atherogenesis under certain conditions.

The mechanism of the antiatherogenic effects of HDL has been extensively summarized in a review and includes reverse cholesterol transport, inhibition of SMC proliferation and sulfated glycosaminoglycan synthesis in human muscle cells.90 HDL also stimulates endothelial repair and arterial EC cell prostaglandin I_2 (PGI_2) synthesis and facilitation of the metabolism of TG-rich lipoprotein and fibrinolysis. Thus increases in the levels of HDL-C clearly protect against atherosclerosis. HDL is increased in association with weight reduction, exercise, niacin administration, and certain other medications.

Inflammatory and rheologic factors. EC synthesize and secrete proteoglycans (Fig. 7).[96] Accumulation of proteoglycans in the intimal atherosclerotic lesions may predispose to further lipid accumulation, calcification, and thrombosis. One of the proteoglycans, heparan sulfate, interacts with antithrombin III, giving EC a nonthrombogenic surface. Basement membranes in diabetic vascular tissue have decreased heparan sulfate content and decreased nonthrombogenic properties, which might contribute to increased vascular wall permeability. Experimental damage of the EC associated with altered rheology and inflammation leads to decreased heparan sulfate interaction with antithrombin III, increased endothelial cell permeability, and accelerated atherosclerosis in experimental animals.

Production of extracellular matrix is regulated by a number of growth factors. For example, angiotensin II, produced by endothelial cells and SMCs, stimulates incorporation of ^{3}H-glycine and other precursor molecules into extracellular matrix glycoproteins and proteoglycans.[97] Angiotensin II induces a rapid induction of expression of the extracellular matrix glycoprotein, thrombospondin. Endothelium-derived proteoglycans bind to and modify LDL so that it becomes more negatively charged, allowing greater recognition by MP and incorporation to form foam cells. Regions of blood vessels that accumulate proteoglycans have a high propensity to accumulate lipid, particularly in areas associated with endothelial regrowth.[96, 97] LDL–proteoglycan complexes

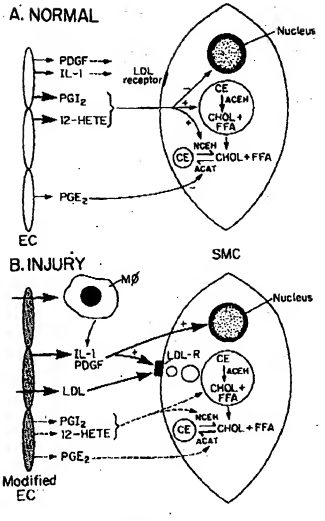

Fig. 8. Alterations in SMC function as result of injury and hyperlipidemia. **A**, Under normal conditions, Endothelial cell *(EC)* and SMC-derived eicosanoids maintain SMC in quiescent state and maintain low cholesterol ester *(CE)* content by stimulating lysosomal *(ACEH)* and cytoplasmic *(NCEH)* cholesterol ester hydrolases. **B**, Under conditions of injury, EC and monocyte release of IL-1 and PDGF causes SMC proliferation, and an increase in the activity of the LDL receptor. In absence of hyperlipidemia, endogenously synthesized eicosanoids may modulate these effects. However, in presence of hyperlipidemia, eicosanoid production is attenuated, leading to unrestricted cell growth and accumulation of CE. *PGI_2*, prostacyclin; *12-HETE*, 12-hydroxy-eicosatetraenoic acid; *CHOL*, cholesterol; *FFA*, free fatty acid; *ACAT*, acyl CoA:cholesterol acyltransferase; *MO*, macrophage. (From Pomerantz KB, Hajjar DP. Arteriosclerosis 1989;9:413-9.)

have been isolated from different regions of extracellular matrix within atherosclerotic vessels. Lipids influence the proteoglycan content of the vascular wall, and proteoglycans, in turn, influence lipid deposition in SMCs and MP.[96] Proteoglycans accompliah this by altering the charge of lipids, decreasing degradation of LDL, and increasing cholesterol ester synthesis by macrophages. Proteoglycans accumulate in intimal lesions of large and small vessels in atherosclerosis and may enhance the calcification associated with increasing complexity of the atherosclerotic lesion. Thus proteoglycans and other extracellular substances contribute significantly to the progression of the atherosclerotic lesion.

Polyunsaturated fatty acids have antiatherosclerotic effects that appear as a result of several mechanisms: (1) modification of the arachidonic acid cascade;[98] (2) reduction of monocyte production of platelet-activating factor,[99] a proinflammatory and proaggregation lipid mediator in atherosclerosis;[99] (3) inhibition of coagulation;[100] (4) reduction in synthesis and action of peptide mediators of cell proliferation including IL-1, TNF,[101] and PDGF[102]; (5) increased formation and/or EDRF;[103] and (6) increased erythrocyte deformity and reduction of blood viscosity.[104] In addition, omega-3 fatty acids in fish oil replace PGI_2 and PGA_2 with PGI_3 and PGA_3, favoring vasodilation and suppression of SMC growth.[96] Thus there are a number of potential mechanisms by which polyunsaturated fatty acids are antiatherosclerotic.

MP synthesize and release growth factors, cytokines, adhesive glycoproteins, prostaglandins, and leukotrienes. Prostaglandin PGI_2 has significant antiatherosclerotic properties. PGI_2 synthesis is reduced in human, rabbit, and rat atherosclerotic blood vessels.[95] Diabetes mellitus reduces PGI_2 synthesis in rats; this effect is additive with that of increased blood cholesterol.[15] This might be related, in part, to decreased arachidonic acid availability for synthesis of PGI_2.[96] Smoking, aging, and viral infections cause decreased vascular eicosanoid synthesis. These eicosanoids, particularly PGI_2 and PGE_2, normally hydrolyze cellular cholesteryl ester, forming free cholesterol, which is more readily removed from the cell. HDL induces PGI_2 production in vascular EC and SMCs, which contributes to HDL-mediated cholesterol efflux. Cholesterol-enriched SMCs (foam cells) synthesize less eicosanoid and thus are not so responsive to the cholesterol-efflux effects of HDL. EC synthesize PGI_2 in response to thrombin, bradykinin, leukotrienes, kallikreins, immune complexes, complement complexes, histamine, serotonin, and angiotensin II.[96] In an autocrine fashion, IL-1 synthesized by the endothelium stimulates the production of PGI_2[105] and tissue plasminogen activation inhibits EC production of PDGF (Fig. 8).[98] EC production of IL-1 in turn increases the production of platelet-activating factors[106] and endothelin.[107] Thus factors produced by EC can modulate the production of other endothelial factors that affect the atherosclerotic process.

SUMMARY

CHD remains the leading cause of death in most developed countries; therefore, elucidation of risk factors and associated mechanisms for atherosclerosis and development of CHD has been a high priority. Data from the Framingham Heart Study and other large-scale epidemiologic studies have identified major risk factors associated with CHD, demonstrating the adverse effects of increased total and LDL-C levels and the protective effect of HDL-C. Other endogenous and exogenous risk factors have been identified and are discussed in this review. In addition, we address known mechanisms involved in the atherosclerotic process.

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